## REMARKS

Reconsideration of this application is requested.

The claims pending in the application are claims 1-11 and 24-27. An obvious error has been corrected in claim 26. Otherwise all of the other claims remain as previously presented.

Initially it is noted that the Examiner has referred to claims 24 and 25 as new claims. See 1st full ¶, page 4 of the action. However, the applicants' new claims in the preceding amendment were claims 26 and 27, not claims 24 and 25. It is presumed that the Examiner meant to refer to claims 26 and 27, not claims 24 and 25. In this regard, it is noted that claims 26 and 27 are specifically directed to the treatment of a common cold by administering to a mammal in need of such treatment, i.e. a mammal that has a cold. Cook et al. do not disclose, expressly or inherently, the treatment of a common cold or the treatment of any mammal that has a cold. Claims 26 and claim 27, therefore, are novel over Cook et al. and should be patentable thereover. The applicants submit that the same conclusion should be drawn with respect to all of the applicants' claims for the reasons set forth herein, including the supporting documentation.

The Examiner has rejected applicants' claims 1-11 and 24-27 under 35 U.S.C. 102(b) as anticipated by Cook et al. U.S. Patent 5,827,885. With respect, the applicants submit that the Examiner's rejection is not correct and should be withdrawn.

Before commenting in detail on the Examiner's rejection, it seems useful to set out the following substantive points:

(1) Anticipation, i.e. lack of novelty, requires that the prior art disclose expressly or inherently, the claimed invention. Cook et al. do not provide such a disclosure expressly or inherently. In particular, Cook et al. do not disclose, expressly or inherently, the treatment of a common cold or its symptoms in a mammal which is in need of such treatment, i.e. a mammal which has a cold or the symptoms thereof. Giving a conjugated fatty acid to a mammal in general is not the same thing as giving the conjugated fatty acid to a mammal with a common cold or the symptoms thereof. Clearly, not everyone has a cold or its symptoms. Hence, the mere administration of a conjugated fatty acid to a human is not the same thing as administering the fatty acid to someone with a common cold or its symptoms.

(2) Rejection of method-of-use claims based on inherency requires that carrying out the prior art necessarily accomplishes the same thing as is claimed. An

inherency rejection cannot be based on a hit or miss possibility that somehow under some possible conditions, the claimed method is accomplished. Rejection on the basis of inherency in the prior art means that practice of the prior art necessarily meets the claimed method. This cannot be the case in the present situation.

(3) The disclosure of a method of treating a virus infection in general or, more specifically, picornavirus, is not the same thing as treating a common cold or the symptoms thereof. Similarly, even the treatment of rhinovirus infection is not necessarily a disclosure, inherently or expressly, of the treatment of the common cold or the symptoms thereof.

(4) The applicants do not argue with the Examiner, or the authorities he refers to, that an old composition remains old and unpatentable as a composition even if new properties of the composition are discovered. However, the new use of the old composition based on the newly discovered properties can be patentable. This is the situation here. The applicants are claiming a new use of the conjugated fatty acids, notably conjugated linoleic acid (CLA) or derivative thereof in the treatment of a common cold or the symptoms thereof. This method is new based on the discovery of new properties in CLA and its derivatives. In this respect, claims to a method-of-use, based on the discovery of novel properties stand in a totally different light patentabilitywise from claims to the composition which may be used in the method.

(5) The authorities relied on by the Examiner are not relevant to the present factual situation. These authorities are, in essence, concerned with situations where compositions were being claimed based on the discovery of new properties. In such situations, the compositions obviously remain old for whatever properties they expressly or inherently possess so that claims to the compositions as such do not define novel subject matter. However, the present case is fundamentally different in claiming the new use of CLA or its derivatives based on a property not hitherto disclosed, i.e. the finding of effectiveness of these compositions in the treatment of a common cold or its symptoms in a mammal. Cook et al. do not disclose, expressly or inherently, this new use discovered and claimed by the applicants.

The applicants submit, for the reasons set out above and detailed below, that Cook et al. do not anticipate the applicants' invention as defined by claims 1-11 and 24-27. Cook et al. simply do not disclose, expressly or inherently, or even suggest, a method of treating a common cold or the symptoms thereof in a mammal by administering a conjugated fatty acid or derivative thereof to a mammal in need of

such treatment. Restated, there is no disclosure or suggestion in Cook et al. of: (i) a mammal having a common cold in need of treatment;(ii) a virus capable of causing the common cold; or (iii) a mammal infected with a virus causing the common cold.

The disclosure of a method for treating the symptoms associated with a viral infection in Cook et al. (Col. 2, lines 25-27) is not novelty destroying for the claimed subject matter because there is no indication that the viral infection is a common cold. Manifestly, a generalized disclosure cannot anticipate a specific disclosure.

The Examiner has tried to rely on the mention of the picornavirus family at Column 9, line 15 of Cook et al. in order to establish the disclosure of a mammal having the common cold. However, the Examiner has simply assumed, incorrectly, that a picornavirus is equivalent to a rhinovirus and furthermore that the rhinovirus actually causes the common cold. This is not what Cook et al. discloses, however, and there is no valid support for the Examiner's assumptions.

In connection with the above, the applicants attach a copy of a page from Introduction to Modern Virology (Dimmock and Primrose, Blackwell Science, 4th Edition, 1994, page 342). This shows that not all picornaviruses are rhinoviruses and that not all rhinoviruses cause infections of the upper respiratory tract. Many picornaviruses are not related to the common cold at all and rhinoviruses are only mainly, i.e., not exclusively, infections of the upper respiratory tract. Robbins Pathologic Basis of Disease, cited by the Examiner, does not state otherwise.

Also attached is a copy of "Picornavirus-Overview" by Larry I. Lutwik ("Lutwik") taken from the eMedicine World Medical Library. At the top of page 2 under the heading "Background", 1st ¶, it is stated that:

> "The viruses in the family *Picornaviridae* (picornaviruses) cause an extraordinarily wide range of illnesses. ... Probably no other family of viruses causes such a diversity of illnesses."

There are references to rhinoviruses on pages 7, 8 and 10 of Lutwik but this does not alter the fact that there is no direction in Cook et al. for a skilled person to (a) select viruses which actually cause the common cold, (b) then infect a mammal with this virus and (c) then select those mammals in which a common cold develops and administer CLA to them.

The applicants also attach a copy of an abstract stating that rhinovirus infection of the lower airways is a recognized disease associated with bronchiolitis and asthma (Dosanjh. A., Acta Biochim Biophys. Sin (Shanghai), 2006 Dec.; 38(12):911-4). Thus, rhinovirus infection does not necessarily cause the common cold but can cause other conditions instead.

Cook et al. do not refer to specific members of the picornavirus family, such as rhinoviruses, let alone mention rhinoviruses that cause the common cold. Cook et al. only disclose virus families, not individual members at Column 9, lines 15-18. Again, a generic disclosure of a family of viruses cannot anticipate a specific disclosure of a virus which causes the common cold.

Finally, Cook et al. do not describe an infection with any virus that results in a mammal catching the common cold. Therefore, Cook et al. cannot disclose the treatment of a mammal having the common cold. A viral infection does not necessarily result in a particular condition if, for example, the host is immune to the virus.

For at least the above reasons, the applicants submit that Cook et al. fail to disclose a method that falls within the scope of the claims.

While the foregoing should be dispositive of the Examiner's Section 102(b) rejection, it is thought to be useful to again remind the Examiner that he has relied on case law dealing with the claiming of compositions, which is not relevant to the claimed method for treating the common cold. As explained above, there is no inherent disclosure of the applicants' new use of CLA in the prior art at least for the reason that there is no disclosure in Cook et al. of a mammal having the common cold or the symptoms thereof.

Finally, the applicants note that the disclosure in Cook et al. is clearly speculative and there is no evidence that CLA is a broad spectrum antiviral agent. Indeed, there is only one example of infection with a virus in Cook et al. and this is for a non-mammal, i.e., the chicks in Example 7 infected with fowl pox virus. Clearly, such limited exemplification underscores the fact that there is no valid basis for extending the Cook et al. disclosure to inherently anticipate the treatment of every possible viral infection in animals. This, in essence, is what the Examiner's rejection attempts to do and it is not, in any sense, appropriate for the reasons noted above.

The Examiner is respectfully requested to reconsider and withdraw the Section 102(b) rejection of the claims. If the Examiner considers that discussion would be helpful, he is requested to telephone the undersigned.

Favorable action is requested.

Respectfully submitted,

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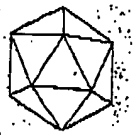
Family: Reoviridae (class III)

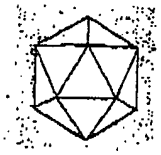


10–12 segments of double-stranded RNA of total $M_r$ $12–20 \times 10^6$. Particle is a 60–80 nm icosahedron. Has an isometric nucleocapsid with transcriptase activity. Cytoplasmic multiplication.

Genera: Reovirus – of vertebrates
Orbivirus – of vertebrates, but also multiply in insects
Rotavirus – of vertebrates
Cytoplasmic polyhedrosis viruses – of insects
Phytoreovirus – clover wound-tumour virus
Fijivirus – Fiji disease of plants

See: Estes, M. K. & Cohen, J. (1989) Rotavirus gene structure and function. *Microbiological Reviews*, 53, 410–449.
Estes, M. K., Palmer, E. L. & Obijeski, J. F. (1983) Rotaviruses: a review. *Current Topics in Microbiology and Immunology*, 105, 123–184.
Joklik, W. K. (1985) Recent progress in reovirus research. *Annual Review of Genetics*, 19, 537–575.
Nuss, D. L. & Dall, D. J. (1990) Structural and functional properties of plant reovirus genomes. *Advances in Virus Research*, 38, 249–306.
Roy, P. & Gorman, B. M. (1990) Bluetongue viruses. *Current Topics in Microbiology and Immunology*, 162, 1–200.

Family: Birnaviridae (class III)

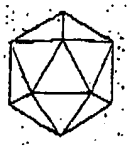


Two segments of double-stranded RNA of $M_r$ $2.5 \times 10^6$ and $2.3 \times 10^6$ in one 60 nm particle. Icosahedral with 45 nm core. RNA transcriptase present. Cytoplasmic.

Genus: Birnavirus (pancreatic necrosis virus of fish; infectious bursal disease of chickens; *Drosophila* X virus)

See: Becht, H. (1980) Infectious bursal disease virus. *Current Topics in Microbiology and Immunology*, 90, 107–121.

Family: Picornaviridae (class IV)



Single-stranded RNA of $M_r$ $2.5 \times 10^6$. Icosahedral particles of 30 nm. Multiplication is cytoplasmic.

Genera: Enterovirus (acid-resistant, primarily viruses of gastrointestinal tract)
Rhinovirus (acid-labile, mainly viruses of upper respiratory tract)
Aphthovirus (foot-and-mouth disease virus)
Cardiovirus (encephalomyocarditis [EMC] virus of mice)
Hepatitis A virus (of humans)
Also various viruses of insects

See: Macnaughton, M. R. (1982) The structure and replication of rhinoviruses. *Current Topics in Microbiology and Immunology*, 97, 1–26.

# Picornavirus-Overview

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**Synonyms and related keywords:** Picornavirus, picornaviruses, Picornaviridae, Rhinovirus, Enterovirus, echovirus, poliovirus, coxsackievirus

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## AUTHOR INFORMATION

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Disclosure





**Background:** The viruses in the family Picornaviridae (picornaviruses) cause an extraordinarily wide range of illnesses. The syndromes associated with these agents include asymptomatic infection, aseptic meningitis syndrome (the most common acute viral disease of the CNS), colds, febrile illness with rash, conjunctivitis, herpangina, muscle infection, heart infection, and hepatitis. Probably no other family of viruses causes such a diversity of illness.

One member of this family, the poliomyelitis virus, was one of the first recorded infections; an Egyptian tomb carving showed a man with a foot-drop deformity typical of paralytic poliomyelitis. Another member of the picornaviruses is the hand-foot-and-mouth disease (HFMD) virus. Bovine foot-and-mouth disease (FMD) is caused by a bovine Picornavirus. That virus does not cause HFMD in humans. The most common cause of the human syndrome is coxsackievirus A16.

**Characteristics**

The viruses of the family Picornaviridae (pico meaning very small, 18-30 nm) all share icosahedral structural symmetry and a genome of single-stranded positive-sense RNA. All members of this family lack a lipid envelope and, therefore, are resistant to ether, chloroform, and alcohol. However, ionizing radiation, phenol, and formaldehyde readily inactivate Picornaviridae. The single-strand RNA molecule ranges from 7.2-8.5 kilobases in size. If protected from nucleases, naked picornaviral RNA can infect cells with a specific infectivity of approximately one millionth of the intact virus.

The viral capsid of picornaviruses consists of a densely packed icosahedral arrangement of 60 protomers. Each protomer consists of 4 polypeptides, etoposide (VP) 1, 2, 3, and 4, which all derive from the cleavage of a larger protein.

The capsid-coat protein serves multiple functions, including (1) protecting the viral RNA from degradation by environmental RNAse, (2) determining host and tissue tropism by recognition of cell-specific cell-membrane receptors, (3) penetrating target cells and delivering the viral RNA into the cell cytoplasm, and (4) selecting and packaging viral RNA.

Two major human genera of Picornaviridae, the enteroviruses and rhinoviruses, have an identical morphology but can be distinguished based on clinical, biophysical, and epidemiological studies.

Enteroviruses grow at a wide pH range (ie, 3-10). After initial replication in the oropharynx, enteroviruses survive the acidic environment of the

stomach and replicate best at 37°C. The small intestine is the major invasion site of enteroviruses.

Rhinoviruses replicate at a pH of 6-8. After initial replication in the nasal passages, the acidic environment of the stomach destroys Rhinovirus. The optimum temperature for rhinoviral replication is 33°C; therefore, this virus primarily infects the nasal passages.

**Classification**

The genus Enterovirus has several subgroups: 3 serotypes of poliovirus, 23 serotypes of group A coxsackieviruses, 6 serotypes of group B coxsackieviruses, and 31 serotypes of echoviruses. These viruses are grouped according to pathogenicity, host range, and serotypes, which are based on serum neutralization. Some enteroviruses are not classified further but assigned a number between 68 and 71. Bovine, simian, and porcine enteroviruses also exist.

Overall, Picornaviridae includes 9 genera. In addition to the major human pathogens of Enterovirus (containing poliovirus, enterovirus, coxsackievirus, echovirus), Rhinovirus (approximately 105 serotypes), and Hepatovirus (hepatitis A virus [HAV]), the family also contains 6 other genera, which include viruses of vertebrate hosts but not human pathogens.

Cardiovirus (type species - encephalomyocarditis virus) is a classic infection in mice. Certain strains of this virus associate with the development of diabetes in certain strains of mice and are used as a model for virus-associated insulin-requiring diabetes in humans.

Aphtovirus (type species - FMD virus) creates a major worldwide economic problem, particularly in South America and Australia. FMD, which has 7 serotypes, is largely controlled by the immunization or slaughter of infected animals. Aphtoviruses are more acid-labile than other picornaviruses.

The other genera include Parechovirus, Erbovirus (equine rhinitis B virus), Kobuvirus (Aichi virus), and Teschovirus (porcine teschovirus). Cricket paralysis virus, Drosophila C virus, and Tussock moth virus are additional unassigned members of the family and are insect viruses.

**Pathophysiology:** The infection pathogenesis is best understood for polioviruses. This pathophysiology is very similar to other picornaviruses, except that the main target organ is affected after the viremia stage. Also, the virus may not spread at all from the initial site (eg, rhinoviruses).

The replicative cycle of picornaviruses is rapid, completing in approximately 8 hours. The exact timing can vary, depending on variables such as pH, temperature, cell type, and number of viral particles that infect the cell. The cycle proceeds in the cytoplasm of infected cells, can even occur in enucleated cells, and is not inhibited by actinomycin D. Although lytic infections are the rule, the HAV can cause nonlytic infections that persist indefinitely.

Cellular protein synthesis declines precipitously after infection, possibly because of the interference with the 5' end of eukaryotic mRNA. A virus-coded, RNA-dependent, RNA polymerase, which produces negative-sense strands, copies the genomic RNA. These strands serve as templates for the positive-sense RNA synthesis.

In most picornaviral infections, infected cells growing in tissue culture can show the characteristic morphologic changes. Within an hour of infection, margination of the chromatin occurs in which the normally homogeneous nuclear material begins to accumulate on the inside of the nuclear envelope. By 2.5-3 hours, membranous vesicles appear in the cytoplasm, beginning around the nuclear membrane and spreading outward. This vesiculation is associated with changes in the permeability of the cellular plasma membrane and eventual shriveling of the cell. Crystals of virus can be observed late in the process. The cytopathic effect appears mediated, at least in part, by a redistribution of lysosomal enzymes.

The antigenic structure of each viral capsid allows it to bind to specific cell membrane components. The virus uses these membrane receptors to enter the target cell. Different viruses use different identifiable receptors, and receptors may vary even among the same genus. For example, most human Rhinovirus strains bind to the intracellular adhesion molecule 1 (ICAM-1), an immunoglobulinlike molecule, but some use a low-density lipoprotein receptor. Families among the picornaviruses may use the same receptor, which may be shared with unrelated viruses.

**Enteroviruses**

Enteroviruses infect humans, primarily through the ingestion of fecally contaminated material (ie, fecal-oral transmission). The ingested virus replicates in susceptible tissues of the pharynx or gut. Studies show enteroviral particles present within the mucosal M cells. Lab technicians can detect enteroviral replication in lymphoid tissue of the small intestine 24-72 hours after ingestion of the virus.

After multiplication in submucosal lymphatic tissues, enteroviruses pass to regional lymph nodes and give rise to a minor viremia that is transient and usually not detectable. During this low-grade viremia, the virus can spread to reticuloendothelial tissue (eg, liver, spleen, bone marrow, more distant lymph nodes).

In subclinical infections, which are the most common, viral replication ceases at this point because it is contained by host defense mechanisms. In a minority of infected patients, further virus replication occurs in these reticuloendothelial sites, leading to major viremia. The major viremia then can result in dissemination to target organs (eg, CNS, heart, skin). In these tissues, necrosis and inflammatory lesions can occur that generally are not found in the gut and lymphoreticular tissues associated with earlier replicative events, an interesting occurrence. In target organs, the degree of inflammatory change and tissue necrosis corresponds to the titer of the infectious virus present. Exercise, cold exposure, malnutrition, pregnancy, immunosuppression by drugs, and radiation can enhance the severity of the infection. Of note, persons with HIV infection may acquire chronic

Enterovirus infections of the meninges.

**Frequency:**

- **In the US:** Overall incidence is unknown. Most enteroviruses survive well in moist or wet environments and, thus, are readily transmitted via the fecal-oral route. Therefore, the viruses are most prevalent in hot countries where they can be endemic year-round and in temperate climates during summer and fall months. This seasonal periodicity is observed in cities of the northern United States but is less pronounced in warmer areas (eg, Atlanta, Miami, disappears altogether in the tropics). Rhinoviruses also have a well-established seasonal pattern that differs from enteroviral-induced infection; in temperate climates, Rhinovirus has fall and spring peaks of infection. Early fall outbreaks of Rhinovirus colds are most characteristic and annually initiate the respiratory disease season. In tropical areas, Rhinovirus outbreaks occur in the rainy season. In the arctic, outbreaks occur during the colder weather.

- **Internationally:** Enteroviruses are distributed worldwide. Global eradication projects indicate that by 1991, scientists eradicated poliomyelitis in the Western Hemisphere. By 1997, the incidence declined to 4000 cases per year, mostly in the developing nations of Sub-Saharan Africa and South Asia.

**Mortality/Morbidity:** The members of Picornaviridae cause a dramatic variety of illnesses. Different viruses produce different clinical pictures, while the same types cause varying manifestations in different individuals.

**Race:** No known racial preference exists.

**Sex:** Some Enterovirus infections, particularly those of the CNS, affect boys more often than girls. After puberty, the reverse is true, perhaps because women have greater exposure to children shedding the virus.

**Age:** Aseptic meningitis is most common in very young infants. Myocarditis and pleurodynia are most prevalent in adolescents and young adults.

- Enteroviruses: The risk of certain enterovirus-related clinical syndromes varies with age and sex. Enteroviral infections occur predominantly in children. For enteroviral infections, antibody prevalence rates measured for a few serotypes indicate that after the decline of passively acquired maternal antibodies after the age of 6 months, the fraction of immune persons in the population rises progressively with age until 15-90% of the adult population have type-specific neutralizing antibodies for each serotype tested. Symptomatic enteroviral infections are uncommon in the elderly population. Approximately 95% of infections caused by poliovirus and at least 50% of enteroviral infections that are not associated with polio are presumed completely asymptomatic.

- Rhinovirus: Prevalence studies of the Rhinovirus antibody show

rapid acquisition of antibody during childhood and adolescence, with peak prevalence in young adults. A slight decrease in the prevalence of antibody in older adults results from lessened viral exposure. Colds are one of the most infectious symptoms in humans. Infection rates range from 1.2 infections per year in children younger than 1 year to 0.7 infections per year in young adults. Approximately 70-88% of Rhinovirus infections are associated with symptomatic respiratory illness.





**History:** The following summary intends to cover general clinical symptomatology for major members of the virus family.

- Enterovirus symptoms
  - Poliovirus: Manifestations of infection range from inapparent illness to severe paralysis and death.
  - Abortive poliomyelitis virus infection is characterized by 2-3 days of fever, headache, sore throat, listlessness, anorexia, vomiting, and abdominal pain. Findings of a neurologic examination are normal.
  - Nonparalytic poliomyelitis differs from the abortive form by the presence of meningeal irritation.
  - Spinal paralytic poliomyelitis has a biphasic course. The minor illness coinciding with viremia corresponds to the symptoms of abortive polio and lasts 1-3 days. The patient then appears to be recovering and remains symptom-free for 2-5 days before the abrupt onset of the major illness. Meningitis is the preparalytic symptom of the major illness. Meningismus and accompanying muscle pain generally are present for 1-2 days before frank weakness and paralysis ensue. The paralysis is flaccid, asymptomatic in distribution. Proximal muscles of the extremities tend to be more involved than distal muscles; the legs are more commonly involved than the arms.
  - Bulbar paralytic poliomyelitis consists of paralysis of muscle groups innervated by cranial nerves, especially those of the soft palate and pharynx, resulting in dysphagia, nasal speech, and some dyspnea.
  - Polioencephalitis is characterized by disturbances of consciousness, occurring predominantly in infants. This condition is the only type of poliomyelitis in which seizures

are common.

- Systemic infections caused by enteroviruses other than polioviruses
  - CNS: Enterovirus 71 is a prominent cause of CNS infections, including encephalitis.
  - Heart: Coxsackievirus B particularly causes acute myocarditis and pericarditis.
  - Skeletal muscles: Epidemic pleurodynia also usually is caused by coxsackievirus B and is characterized by fever and severe pain in the chest. If the diaphragm is involved, severe pain develops in the abdomen. Symptoms last for a few days to 2 weeks and resolve without ill effects. In another syndrome, myalgic encephalomyelitis (ME), patients have few, if any, physical signs; but many symptoms develop. The most prominent symptoms are fatigue, following even minor physical activity, and depressive psychological illness.
  - Skin and mucous membranes: Enteroviral infections of these tissues are caused almost entirely by coxsackievirus A. Rashes may accompany infections of other systems. Herpangina is a painful infection of the pharynx with herpeslike features (eg, vesicles of the soft palate, fauces, uvula, posterior wall of the pharynx). The infection resolves spontaneously in a few days. In HFMD unrelated to the FMD of cattle, vesicles and ulcers are present in the anterior part of the mouth, followed by a vesicular rash on the hands and feet.
  - Conjunctiva: Infection is characterized by subconjunctival hemorrhage, severe pain in the eyes, photophobia, and occasional keratitis. Coxsackievirus A24 and echovirus 70 are the main causes of this infection.
- Rhinoviruses
  - Rhinoviruses produce a typical common cold that usually lasts no more than 7 days.
  - In most cases, rhinorrhea and nasal obstruction are the most prominent complaints.
  - A sore or scratchy throat frequently is present. Cough and hoarseness occur in 33% of all cases.
- Hepatitis A
  - HAV has an incubation period of 2-6 weeks, with an average of 28 days. Many infections are silent, particularly in small children.
  - Clinical illness usually starts in a few days, with symptoms of

malaise, anorexia, vague abdominal discomfort, and fever. Later, the urine becomes dark and the feces appear pale.

- Soon afterwards, jaundice appears, first in the sclera and then in the skin; if severe, itching may accompany these symptoms. The patient starts to feel better within the next week or so, and the jaundice disappears within a month.

**Physical:**

- The end of the nose may have a red color with clear, mucoid, nasal secretions.
- A chest examination may reveal the sound of rhonchi.

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Herpes Simplex
Meningitis

**Other Problems to be Considered:**

**Poliomyelitis**

Guillain-Barré syndrome
Meningitis caused by other viruses
Meningitis caused by bacteria
Encephalitis from other viruses or bacteria

**Other enteroviral systemic infections**

Heterophile-negative mononucleosis
Herpes simplex type I
Aphthous stomatitis
Bacterial tonsillitis

**Rhinoviruses**

Colds caused by other viruses
Bacterial upper respiratory infections

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**Lab Studies:**

- Viral isolation through cell culture

- Sample multiple sites to optimize the opportunity to recover a virus in cell culture.
- Late in the course of enteroviral illness, use viral cultures of feces because the lower intestine may be the only site still excreting the agent. Confirm an etiologic diagnosis by isolating the virus from cerebrospinal fluid (CSF), pericardial fluid, tissue, or blood, depending on the clinical syndrome. Remember that isolating an Enterovirus from the stool does not necessarily signify that a systemic or focal illness is caused by that virus; in fact, that virus may be an innocent bystander and not related to pathology elsewhere. Pharyngeal secretions should always be cultured in addition to feces.
- Isolate rhinoviruses at the optimum temperature of 33-34°C.
- With the identification of a characteristic cytopathic effect in any 3 or 4 appropriately chosen cell lines, the laboratory can report a presumptive diagnosis of enteroviral infection within 2-5 days.
- In the future, genomic sequencing likely will characterize enteroviral strains.

- Polymerase chain reaction
  - To detect enteroviral RNA in clinical specimens, use reverse transcriptase polymerase chain reaction (RT-PCR), which is rapid, sensitive, and specific.
  - RT-PCR can detect enteroviral RNA from CSF, throat swabs, serum, urine, and stool. It also can detect enteroviral RNA in the endomyocardial biopsy specimen from cases of acute myocarditis.
- Serology
  - The optimal use of antibodies for the diagnosis of picornaviral infections involves acute and convalescent serum, which should, if possible, be run in parallel. A single high-antibody result can be misleading.
  - The microneutralization test is the most widely used method for the determination of antibodies to enteroviruses.
  - During its acute stage, viral hepatitis can be diagnosed based on liver dysfunction, as indicated by raised serum bilirubin and aminotransferases.
- Physicians usually make the specific diagnosis of HAV by performing an enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay test for specific immunoglobulin M (IgM).



**Medical Care:**

- Poliomyelitis
  - Specific antiviral agents for the treatment of poliomyelitis are not available; therefore,

management is supportive and symptomatic.

- In the acute phase of paralytic poliomyelitis, hospitalize the patient. Bed rest prevents the augmentation or extension of the paralysis. Early data in an animal model suggest that exercise early during infection can heighten the paresis
- Applying hot moist packs to muscles can help relieve pain and muscle spasm.
- Paralysis of the respiratory muscles necessitates mechanical ventilation before severe hypoventilation develops.
- Severe bulbar paralysis necessitates tracheal intubation.
- Weakness or paralysis of the bladder necessitates catheterization.

• Other systemic enteroviral infections

- Due to the lack of specific antiviral therapy, clinicians manage most enteroviral illnesses symptomatically.
- Specialists successfully treat some immunocompromised patients with persistent enteroviral infections using immunoglobulins. This is the case with most patients who have agammaglobulinemia and echovirus meningoencephalitis and who benefited from immunoglobulin-containing antibody against the involved echovirus.
- Although effective antiviral therapy is not yet clinically available, some promising antienteroviral drugs reduce the duration of illness among adults with enteroviral aseptic meningitis.

• Hepatitis A

- At present, no specific therapy is available for HAV, and management is totally supportive in nature.
- Explain dietary recommendations to the patient, including the avoidance of other potentially hepatotoxic substances (eg, medications, ethanol).
- Hospitalize and offer supportive treatment to any patient with a rare case of fulminant hepatitis manifested by hepatic encephalopathy with or without coagulopathy. True chronic infection with HAV is not well documented.
- Consider liver transplantation for patients who have a poor prognosis with medical management alone.

• Rhinovirus

- Symptomatically care for fever and rhinitis, which is effective treatment for Rhinovirus colds.
- Start treatment as early as symptoms are recognized, and continue every 12 hours for 4-5 days.

- Rest, hydration, nasal decongestants, and cough suppressants also may be appropriate.
- Regularly apply petrolatum-based ointment to help prevent painful macerations on the nares.
- Administer antimicrobial therapy to patients with secondary bacterial sinusitis or otitis media.





**Deterrence/Prevention:**

- The poliovirus immunization strategy in the United States: According to the latest recommendation, inactivated poliovirus vaccine (IPV) must be used in the childhood immunization schedule, while permitting live-attenuated poliovirus vaccine (OPV) only for travel to polio-endemic regions for those patients in whom only 1 dose of polio vaccine can be given before protection is required.
- Poliomyelitis vaccine
  - Physicians use (ie, for >30 y) both IPV and OPV.
  - The protocol recommended for IPV is to administer 4 doses in a child at age 2 months, 4 months, 6-18 months, and 4-6 years. The efficacy of IPV after 1-2 doses is lower than the equivalent number of OPV doses.
  - The protocol recommended for OPV is 4 doses in a child at age 2 months, 4 months, 6-18 months, and 4-6 years. The only disadvantage of OPV is the very rare occurrence of vaccine virus-associated poliomyelitis (ie, 8 cases annually in US). The mechanism by which the OPV viruses cause rare cases of paralytic disease is not fully understood.
- Populations recommended to receive HAV vaccine preexposure prophylaxis include the following:
  - Patients older than 2 years who are at increased risk for infection
  - Populations at increased risk of infection
  - Persons traveling to work in countries with high epidemicity
  - Children in communities that have high rates of disease and periodic outbreaks
  - Men who have sex with other men
  - Users of illegal drugs
  - Persons who have an occupational risk for infection
  - Patients with chronic liver disease or clotting factor deficiencies

- Those patients who work directly with the virus, including sewage workers, plumbers, primate handlers, medical and nursing staff, and daycare center staff

- Populations recommended to receive immunoglobulin vaccine for HAV after exposure or as an alternative for an HAV vaccine include the following:
  - Patients exposed to HAV in the past 14 days who may be susceptible to the disease
  - Household and sexual contacts of known cases
  - Staff and attendees of daycare centers or homes after 1 or more cases occur in children and employees or 2 or more cases occur in the household of attendees
  - Fellow food handlers
  - Those at risk who work in schools and hospitals or other work settings
  - Any patient with suspected exposure under outbreak situations
  - Patients in outbreak situations with suspected exposure
  - Children younger than 2 years
  - Not recommended for patients with casual contact with 1 case

**Complications:**

- Hepatitis A virus
  - Cholestasis
  - Relapsing disease
  - Fulminant hepatitis
  - Chronic, active autoimmune hepatitis
- Enterovirus
  - Respiratory compromise is caused by paralysis of the respiratory muscles, by airway obstruction from involvement of cranial nerve nuclei, or by respiratory center lesions.
  - GI events (eg, hemorrhage, paralytic ileus, gastric dilation) may complicate acute paralysis.
- Superimposed bacterial sinusitis
- Bacterial otitis media
- Precipitation of asthma

**Patient Education:**

- For excellent patient education resources, visit eMedicine's Cold and Flu Center. Also, see eMedicine's patient education article Colds.

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**Medical/Legal Pitfalls:**

- Poliomyelitis
  - Because of the small but finite potential of vaccine virus-associated poliomyelitis, medicolegally it is prudent to not use OPV when the current enhanced immunogenicity-killed vaccine is available. If rapid action is needed (as in immediate travel to an endemic area), live-attenuated vaccine may be used.
  - The recent (late 2000) recognition of an outbreak of vaccine viruslike poliomyelitis in the Dominican Republic and Haiti occurred in a population with a poor adherence to routine immunization. Public health officials worldwide should be aware of this and attempt to booster overall immunity to poliovirus.
  - Under no circumstance should immunocompromised individuals receive OPV.
  - Fetal risk is poorly documented in cases where OPV is given during pregnancy. In the past, this vaccine has been given during pregnancy if the potential of prevention of polio is substantial.
  - All potential cases of poliomyelitis should be reported promptly to local public health officials.
- Hepatitis A
  - Prompt recognition of HAV infection is needed to institute passive (immunoglobulin) and/or active (vaccine) treatment to prevent secondary cases in the family or daycare setting.
  - Public health officials should be contacted if a case of hepatitis A is suspected or diagnosed in a food handler so that appropriate notifications of potentially exposed individuals can be made promptly.
  - Recent recommendations in the United States have made hepatitis A vaccine part of routine well-baby immunizations in children living in states or areas with a higher incidence of the infection, primarily in the western United States.

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## Transforming growth factor-beta expression induced by rhinovirus infection in respiratory epithelial cells.

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Rhinovirus infection of the lower airways is now a recognized disease, associated with bronchiolitis and asthma. The bronchial epithelial cells are the host cells when rhinovirus infection occurs in the airway. It was hypothesized that a pro-fibrotic growth factor response may occur in these infected cells, leading to production of a key transforming growth factor, TGF-beta-1. Bronchial epithelial cells were inoculated with human rhinovirus and compared at day 1, 3 and 5 to control non-infected cells. Cell culture supernatant fluid and cellular RNA were isolated. The amount of released TGF-beta protein was measured by enzyme-linked immunosorbent assay (ELISA). Expression of TGF-beta at the level of transcription was measured by polymerase chain reaction (PCR) and gel electrophoresis. The results show that at all time points studied, TGF-beta production is greater in the infected cells, as demonstrated by ELISA ($P<0.05$) and by semi-quantitative PCR analysis. It was concluded that bronchial epithelial cells infected with common cold virus and rhinovirus, showed higher levels of TGF-beta. The production of TGF-beta may be indicative of a normal repair mechanism to counter inflammation, or in the setting of persistent asthma, could potentially lead to increased fibrosis and collagen deposition.

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